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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/477,962	01/05/2000	BEN SHEN	2500.125US2	9979

7590 03/12/2002

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EXAMINER	
KERR, KATHLEEN M	

ART UNIT	PAPER NUMBER
1652	13

DATE MAILED: 03/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/477,962	SHEN ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-73* is/are pending in the application.

4a) Of the above claim(s) *6-8,22,24-39 and 46-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9-21,23,40-45 and 71-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Alignment* .

DETAILED ACTION

Application Status

1. Claims 1-73 are pending in the instant application. The instant Office action is in response to Applicants' election (see below) (Paper No. 12 filed on December 10, 2001). The Examiner notes that Applicants have incorrectly noted the Examiner of the instant application; the examiner is Examiner Kathleen Kerr.

Election

2. Applicants' election with traverse of SuperGroup A, Claims 1-21, 23, 40-45, 65-66, 68-69, and 71-73, Group 1, relating to ORF8 in Paper No. 12 is acknowledged.

The traversal is on the ground(s) that no serious search burden exists to examine all SuperGroups delineated in Paper No. 9. This is not found persuasive because the search burden to examine *any* two Groups, each being from a different SuperGroup, is evidenced in the distinct class/subclass classifications as previously noted:

SuperGroup A members in class 435, subclass 252.3,

SuperGroup B members in class 435, subclass 183,

SuperGroup C members in class 435, subclass 15,

SuperGroup D members in class 435, subclass 76, and

SuperGroup E members in class 435, subclass 15.

When the class/subclass classification is different, a search of any Group will **not** be co-extensive with another Group in the patent literature; searches that are not co-extensive are burdensome on the Examiner. Additionally, a search burden to examine a Group from

SuperGroup C and a Group from SuperGroup E (having the same classification) results from the fact that these groups of methods contain distinct method steps using distinct reagents to produce distinct products. Thus, the methods of SuperGroup C and SuperGroup E would require a wholly different textual search in non-patent literature databases; these searches would not be co-extensive, and thus, burdensome. Moreover, the Examiner specifically noted the possibility of rejoinder in the written restriction requirement. Based on *In re Ochiai*, any methods of making or using a patentable product would be rejoined at a later time in prosecution; methods claims in SuperGroups C, D, and E will be rejoined if patentable products are used in these methods.

The traversal is also on the ground(s) that the restriction between the open reading frames (ORFs), as found in a single claim, is legally improper. Applicants cite *In Re Weber, Soder, and Boksay* saying that the Office cannot restrict within a single claim, irrespective of the Markush-type language. This is not found persuasive. The Examiner reiterates Applicants' citation from *In Re Weber, Soder, and Boksay*:

> If, however, a single claim is required to be divided up and presented in several applications, that claim would never be considered on its merits. The **totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim**. Further, **since the subgenera would be defined by the examiner rather that the applicant**, it is not inconceivable that a number of the **fragments would not be described** in the specification." (emphasis added)

Firstly, the "fragmentary" claims, as implied by the restriction requirement, taken together **WOULD** be the exactly equivalent in scope to the original, single Claim 1. Claim 1 is drawn to **ANY ONE** of the open reading frames, not to any group or groups of them. Additionally, for claims like Claims 2 and 3 which encompass more than one ORF, Applicants can maintain *exactly* the same scope when said claims are written, for example, as ---A nucleic acid

comprising ORF 8 and at least one additional ORF---, etc. For such a claim, the search can be limited to ORF 8, provided that not art is identified for ORF 8, to ease the Examiner's search burden while maintaining *exactly* the scope in Applicants' pending claims. Secondly, **APPLICANTS HAVE DEFINED THE SUBGENERA** in both the specification and, most convincingly, in the claims themselves. The Examiner has not divided the claims arbitrarily, but rather has divided the claims as Applicants have described in their specification and as Applicants have *exactly* claimed in their claims which claim "any **one** of *Blm* open reading frames 8 through 41" (emphasis added).

Applicants argue that the Examiner should have imposed an election of species of the Markush-type claims. This is not found persuasive. Markush-type claims ***must*** have unity of invention; "unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility" (see M.P.E.P. § 803.02). In the instant case, the open reading frames ***do*** share a common utility; however, they **DO NOT SHARE A COMMON STRUCTURAL FEATURE**. Election of species can be utilized when some generic claim can be effectively searched based on a common structural feature. In the instant case, each of the individual open reading frames requires a unique, complete, full-length search in not only sequence databases, but also in textual databases using keywords. In other words, no generic search can effectively be performed on the entirety of Claim 1 as written.

Applicants argue that "the restriction between ORFs improperly contravenes M.P.E.P. § 803.04" and that at least ten ORFs should reasonably be examined together. This is not found persuasive. M.P.E.P. § 803.04 states that "nucleotide sequences encoding the same protein are

not considered to be independent and distinct inventions and will continue to be examined together." Thus, while nucleotide sequences encoding the same protein are **not** considered independent and distinct, they **are** considered different nucleotide sequences. Therefore, where Applicants claim any ORF encoding, for example, a 100-amino acid protein, at least 100^4 different nucleotide sequences are searched (based on the third base pair of any triplet codon encoding an amino acid, said third base pair being the "wobble" base that can be any one of the four nucleotides (A, G, C, T) while maintaining the integrity of the encoded protein). Moreover, when the claimed DNA varies in sequence, such as in claiming "a nucleic acid amplified by PCR using any of the primer pairs identified in Table II", again more than one nucleotide sequence is searched. Thus, with each Group, as divided by the Examiner in Paper No. 9, Applicants are receiving the examination of many, many more than 10 nucleotide sequences.

Even if Applicants disagree with the above interpretation of M.P.E.P. § 803.04, the Examiner maintains that **examining any more than one ORF nucleotide sequence is considered unreasonable** in the instant case. While "normally ten sequences constitute a reasonable number", the instantly claimed sequences contain a *tremendous* amount of variation in claim language like "a nucleic acid amplified by PCR using any of the primer pairs identified in Table II". The Examiner notes that "the complex nature of the claimed material ... may necessitate that the reasonable number of sequence to be selected be less than the" as per M.P.E.P. § 803.04. The Examiner maintains that the claimed material is extremely complex and warrants a reasonable number of sequences being only one.

The requirement is still deemed proper and is therefore made **FINAL**. Claims 1-73 are pending in the instant application. Claims 22, 24-39, 46-64, 67, and 70 are withdrawn from

consideration as non-elected inventions. Thus, Claims 1-21, 23, 40-45, 65-66, 68-69 and 71-73 will be examined herein.

Priority

3. The instant application is granted the benefit of priority for the U.S. Provisional Application No. 60/115,435 filed on January 6, 1999 and 60/118,848 filed on February 5, 1999 as requested in the declaration and the first lines of the specification.

4. Concerning the content of the priority document U.S. Provisional application 60/115,435, the Examiner notes that 60/115,435 does not contain any sequence information although ORFs 1-33 are apparent in figures. Presumably, sequencing had been completed to identify these ORFs. ORF 8, as named in the claims presently (without SEQ ID NO delineation), has priority to this earliest date.

Concerning the content of the priority document U.S. Provisional application 60/118,848, the Examiner notes that 60/118,848 contains *some* sequence information, particularly ORFs 8-32, and the primer pairs for said ORFs as found in Table II of the instant application. However, the Examiner notes that the sequence of ORF 8, as described on pages 71-72 of 60/118,848 is **not the same** as the sequence of ORF 8 in the instant specification that encodes SEQ ID NO:115 and that is SEQ ID NO:1, base pairs 57583-58854 (see attached alignment). 60/118,848 does correctly disclose the same primer pairs for ORF 8 as found in instant Table II. Applicants must explain this apparent discrepancy. Moreover, such an explanation will be helpful if Applicants amend the claims to contain SEQ ID NOs, which sequence information was not disclosed in either priority document in its entirety.

Information Disclosure Statement

5. The information disclosure statement filed on December 6, 2001 (Paper No. 10) fails to comply with 37 C.F.R. § 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The following references were not considered for the reasons described below:

a) Other Document AP: a copy is missing.

b) Other Document AK: the citation is incorrect; the journal name is omitted.

All other documents in said Information Disclosure statement were considered as noted by the Examiner initials in the copy attached hereto.

6. The Examiner notes that several patent documents are noted throughout the specification although none are disclosed by Applicants as being pertinent to the claimed subject matter. None of these documents will be on the face of the patent unless Applicants file them in a supplemental information disclosure statement.

Drawings

7. The drawings are considered informal for the reasons detailed in the attached copy of PTO Form 948. Appropriate correction is required prior to allowance.

Sequence Rules Compliance

8. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2).

However, this application fails to **fully** comply with the requirements of 37 C.F.R. § 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

a) The description of Figure 8C does not particularly point out which SEQ ID NO is the nucleotide sequence disclosed and which is the amino acid sequence disclosed.

Appropriate clarification of the sequences is required.

9. The sequence listing, specifically related to the DNA of the gene cluster, is confusing because the references to various accession numbers and the division of the entire gene cluster between SEQ ID NOs: 1 and 2. Moreover, the positions of ORFs noted in the specification are unclear due to this division. Clarification of the definition of the gene cluster sequence in the sequence listing is required.

Objections to the Specification

10. The specification is objected to for being confusing in the description of the drawings, particularly as follows:

a) In the description of Figure 6, Figures 6A-6F must be described separately.

b) The description of Figure 9 mentions underlining while none is found in the figure.

c) In the description of Figure 11, Figures 11A-11D must be described separately.

d) On page 19, line 14, the accession numbers "AT-149091" and "AT-210249" are unclear. These numbers cannot be identified in GenBank. Also, there are three accession numbers referencing 2 SEQ ID NOs – the correlation is unclear.

e) In Table I on page 19, SEQ ID NOs of the amino acid sequences would be helpful.

f) Also in Table I, the accession number "AA07904.1" is unclear and cannot be identified in GenBank.

g) In Table II, the "position" reference is unclear since the gene cluster is apparently divided between SEQ ID NOs: 1 and 2.

h) On page 47, line 19, the reference to "(18)" is unclear.

i) On page 69, the following accession numbers are unclear: "AL008967", "AL031107", and "AL049863". These numbers cannot be found in GenBank.

j) On page 70, line 29, the reference to "(FIGURE)" is unclear.

Appropriate corrections and/or clarification of all of the above points are required.

Claim Objections

11. Claims 1-21, 23, 40-45, 65-66, 68-69, and 71-73 are objected to for containing non-elected subject matter, particularly as follows:

a) Claims 1-5 (independent Claim 1) are drawn to nucleic acid sequences of ***any one*** of ORFs 8-41, while only ORF 8 is elected.

b) Claims 6-8 (independent Claim 6) are drawn to nucleic acid sequences that encode NRPSs that are wholly distinct from the nucleic acid sequence encoding the oxidase that is ORF 8. Claims 6-8 will not be treated further on their merits as non-elected inventions.

c) Claims 9-15 (independent Claim 9) are drawn to nucleic acid sequences encoding ***any*** protein from the BLM gene cluster while only ORF 8 is elected.

d) Claims 16-18 (independent Claim 16) are drawn to nucleic acid sequences hybridizing to ***any*** ORF listed while only ORF 8 is elected.

e) Claims 19-20 (independent Claim 20) are drawn to nucleic acid sequences that are variants of ***any*** ORF listed while only ORF 8 is elected.

f) Claims 21 and 23 contain ***no specific reference*** to ORF 8; however, said claims will be examined as if the nucleic acid sequences claimed must contain ORF 8.

g) Claims 40-45 claim non-elected subject matter as noted above for Claims 1-21 and 23.

h) Claims 65-66 and 68-69 claim or are related to nucleic acid sequences that are ***not ORF 8***. Claims 65-66 and 68-69 will not be treated further on their merits as non-elected inventions.

i) Claims 71-73 contain ***no specific reference*** to ORF 8; however, said claims will be examined as if the cells claimed must contain a modified ORF 8.

As noted above, Claims 6-8, 65-66, and 68-69 will not be treated further on the merits as non-elected inventions since their subject matter is wholly separate from the elected subject matter. Thus, Claims 1-5, 9-21, 23, 40-45 (except as relating to Claims 6-8), and 71-73 will be examined herein.

12. Claim 72 is objected to for containing a typographical error. In line 2, the word "bene" is misspelled and should be ---gene---.

13. Claim 42 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 42, as it ultimately depends from Claim 21, does not further limit the subject matter of Claim 21 that already requires nucleic acid sequences sufficient for bleomycin production.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1-5, 9-20, 23, 40-45, 71-73 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In each of the instant claims, the term "nucleic acid" is used when apparently referring to ---nucleic acid sequences---. Nucleic acids are small molecules while linear sequences of nucleic acids encode proteins and are useful molecular biological tools. Another equivalent term to "nucleic acid sequences" is ---polynucleotides---.

15. Claims 1-5 and 40-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The structure/indentations of Claim 1 are unclear by the use of tab formation. The Examiner suggests using symbols, such as a), b) and c), to identify items in the Markush group of Claim 1.

16. Claims 1-5 and 40-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "encoding" in Claim 1, line 3 is unclear. Typically in the art, this term is limited to DNA-protein relationships as claimed in lines 5-6. It is unclear is the scope of lines 3-4 is equivalent to lines 5-6, or if lines 3-4 is intended to claim exactly a nucleic acid sequence that is ORF 8, that is SEQ ID NO:1, bases 57583-58854.

17. Claims 1-5, 10-20, and 40-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims contain reference to a specific sequence that is ORF 8. It is unclear if these references are drawn to specific SEQ ID NOs, such SEQ ID NO:1, base pairs 57583-58854, and such as encoding the protein that is SEQ ID NO:115. If these sequences are intended, the SEQ ID NO designation should be used in the claims.

18. Claims 1-5 and 40-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear how "the nucleic acid of a bleomycin-producing organism" can be used as a template since, as noted above, nucleic acids are small molecules while linear sequences of nucleic acids encode proteins and are useful molecular biological tools.

19. Claims 2-5, 10-15, 20, and 40-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "said nucleic acid" has unclear antecedent basis since the term "nucleic acid" is used in many capacities in the parent claims. The Examiner suggests claim language using "An isolated nucleic acid sequence" in the preamble and "comprising a polynucleotide" elsewhere in the claims. Great care must be taken to avoid multiple antecedent basis problems.

20. Claims 9-15 and 40-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 9, the phrase "**a** BLM gene cluster" (emphasis added) is unclear. The article "a" indicates *any* gene cluster where only a single gene cluster is described in the specification implying a single gene cluster, and not one of many, is the subject matter of the instant claims.

21. Claims 9-15 and 40-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 9, the phrase "a **BLM** gene cluster" (emphasis added) is unclear. The abbreviation "BLM" must be defined upon its first appearance in the claims. The Examiner suggests replacing this term with ---bleomycin (BLM)--- for clarity.

22. Claims 16-18 and 40-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The optional domains in Claim 16 are varied while the elected ORF 8 is only disclosed as containing an oxidase domain. It is unclear for ORF 8, or a DNA hybridizing to ORF 8 might contain, for example, a peptidyl carrier protein (PCP) domain. Moreover, Claim 17 is wholly unclear since the oxidase domain of ORF 8 is not disclosed as containing a module.

23. Claims 16-18 and 40-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 16, the metes and bounds of the nucleic acid sequence encoding the noted domains is unclear. The actual "ends" of such domains, when described only vaguely by catalytic function or homologous function, is not definite.

24. Claims 16-18 and 40-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 16, the term "stringent conditions" is unclear as to its metes and bounds. The definition found on page 10 described "preferential" hybridization to its target. However, the term "stringent" in the art has a particular connotation of conditions. While Applicants can be their own lexicographers, the definition noted in the specification cannot be repugnant or misleading with respect to the art-defined term.

25. Claims 21 and 40-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 21 and 42, the term "a bleomycin" is unclear. Bleomycin is a single compound. Does this term claim this single compound or this compound plus analogs of bleomycin? What are the metes and bounds of the analogs as found in Claim 42?

26. Claims 40-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 40 depends from Claim 22 that is not a nucleic acid, but a polypeptide. Thus, Claims 40-45, as they depend from Claim 22, are confusing.

27. Claims 72-73 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "a resistance gene from the bleomycin gene cluster" is unclear, especially as referenced in Table III, since no Table III is found in the specification and no definition of such a gene is found.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

28. Claims 1-5, 16-18, and 40-45 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1 and 16 are drawn to nucleic acid sequences ***related*** to ORF 8 by virtue of the limited structural requirements of primer pairs, as in Claim 1, or hybridization, as in Claim 18. No relation between the claimed structure and the described function is in the claims. Claims 2-5 can be omitted from this rejection if the antecedent basis of "nucleic acid" is made clear in these claims.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed.

Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

The instant specification discloses polynucleotides related to ORF 8. Applicants have fully described the genus relating to a portion of SEQ ID NO:1 (that which encodes SEQ ID NO:115) with both sequence (structural) limitations and functional limitations (i.e., encoding an oxygen-independent coproporphyrinogen III oxidase). However, the genus of the instant claims also contains polynucleotides within the sequence limitations, but having different function. Applicants have not fully described a genus that has sequence identity limitations in the absence of functional limitations.

29. Claims 9-15, 21, 23, 40-45, and 71-73 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 9, 21, 23, and 71 are drawn to nucleic acid sequences claimed according to function alone.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a

precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, ORF 8 and the bleomycin gene cluster as described by a single, specific example that is SEQ ID NOs: 1 and 2. The function of ORF 8 is, in fact, hypothesized by virtue of the Gapped-blast comparison as shown in Table II. However, in the instant claims, these nucleic acids are only described according to the functional characteristics of the enzymes they encode; no structural relationship is described or used in the claims. Thus, one of skill in the art would be unable to predict the structure of other members of this genus by virtue of the instant disclosure. Therefore, claims drawn to the genus of said nucleic acid sequences are also not adequately described.

30. Claims 19 and 20 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application

was filed, had possession of the claimed invention. Although the genus of allelic variants, particularly SNPs, is discussed in the specification, there is no evidence that any representative species of such a large and varied genus was in the possession of the inventors at the time of filing. To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. The specification does not disclose any representative species of any variants, with or without identifying characteristics. One of skill in the art would be unable to predict the structure of the nucleic acid sequences of the genus using only the disclosure provided. Therefore, Claims 19 and 20, as written, fails to satisfy the written description requirement.

31. Claims 1-5, 9-20, and 40-45 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for nucleic acid sequences encoding proteins with the oxidase function as described in the specification for ORF 8, does not reasonably provide enablement for nucleic acid sequences within the claimed structural limitations but having different functions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The use of such polynucleotides would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

While this genus of polynucleotides can be produced, the use of polynucleotides with functions other than those ascribed by the specification would require experimentation. The specification offers no guidance of working examples of such experimentation. The function of the described sequence that is ORF 8 is predicted via homology studies based on the linear sequences. With great variety available to the structure of the sequences, the predictability of the function of the claimed sequences is very low. Without knowing the function of the sequences,

they cannot be used effectively. Thus, one of skill in the art would be required to perform undue experimentation to use the claimed invention with the scope of the instant claims.

32. Claims 21, 23, and 71-73 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for nucleic acid sequences specifically disclosed in the specification, does not reasonably provide enablement for nucleic acid sequences described according to function only without adequate means of testing for such nucleic acid sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The production of such polynucleotides would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized above.

The instant polynucleotides and cells are claimed only by function. A single example of these functions is described in the specification. The specification presents no guidance or working examples in the manipulation of the sequences while retaining the described functions. The overall framework of the sequences, functional domains, etc., is not clear. Thus, one of skill in the art would be required to perform random alterations in the sequences and/or cells followed by testing for bleomycin production. Due to the very complex nature of bleomycin biosynthesis, the nature of such experimentation is extremely tenuous. The ability to produce other polynucleotides and/or host cells meeting the claimed limitations is highly unpredictable due to this variance. Thus, the instant claims are not enabled to the full extent of their scope.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. § 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. § 122(b). Therefore, this application is examined under 35 U.S.C. § 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. § 102(e)).

33. Claims 23, 40, 41, and 43-45 are rejected under 35 U.S.C. § 102(e) as being anticipated by Schupp *et al.* (USPN 6,121,029). The instant claims are drawn to nucleic acid sequences encoding multi-functional protein complexes containing PKS and NRPS proteins; the claims are also drawn to vectors thereof and *Streptomyces* host cells thereof.

Schupp *et al.* teach the epothilone PKS gene cluster; said gene cluster encodes PKSs and an NRPS (see column 18, lines 45-70, particularly EPO P). Schupp *et al.* also teach the epothilone PKS gene cluster in vectors transformed into *Streptomyces* host cells (see column 20, line 18 and column 22, line 22). The effective filing date of Schupp *et al.* is June 18, 1998.

34. Claims 16, 17, 40, 41, and 43-45 are rejected under 35 U.S.C. § 102(b) as being anticipated by Redenbach *et al.* (A set of ordered cosmids and a detailed genetic and physical map for the 8 Mb *Streptomyces* coelicolor A3(2) chromosome. Mol Microbiol 1996 Jul;21(1):77-96). The instant claims are drawn to nucleic acid sequences, vectors, and *Streptomyces* host cells that encode an oxygen-independent coproporphyrinogen III oxidase.

Redenbach *et al.* teach a DNA sequence that encodes a protein that is 34% identical to SEQ ID NO:115 (see attached alignment); such a DNA sequence will hybridize to ORF 8 under stringent conditions, as defined in the specification. Redenbach *et al.* also teach vectors and *Streptomyces* host cells for complementation studies of the disclosed genes (see Abstract).

Additional Art of Record

35. The following references are not used in art rejections but are considered noteworthy by the Examiner:

a) Shen *et al.* Bleomycin biosynthesis in *Streptomyces verticillus* ATCC15003: The search for a hybrid polyketide and peptide biosynthetic system. Book of Abstracts, 217th ACS National Meeting, Anaheim, CA, March 21-25 (1999). ORGN-153.

b) Du *et al.* Bleomycin biosynthesis in *Streptomyces verticillus* ATCC15003: A model for hybrid polyketide and peptide biosynthesis. Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30 (2000). ORGN-822.

c) Du *et al.* The biosynthetic gene cluster for the antitumor drug bleomycin from *Streptomyces verticillus* ATCC15003 supporting functional interactions between nonribosomal peptide synthetases and a polyketide synthase. Chem Biol 2000 Aug;7(8):623-42.

d) Shen *et al.* The biosynthetic gene cluster for the anticancer drug bleomycin from *Streptomyces verticillus* ATCC15003 as a model for hybrid peptide-polyketide natural product biosynthesis. J Ind Microbiol Biotechnol 2001 Dec;27(6):378-85.

Claim Language Suggestions

36. The following are not rejections, but are the Examiner's suggestions for more suitable claim language to better align the instant claim language with terms of art. While the instant claim language meets the statutory threshold of clarity and precision, a more suitable expression of the claimed subject matter is suggested. Such suggestions are encouraged in M.P.E.P. § 2173.02. Claiming the elected nucleic acid sequences and its related products is best exemplified by the following hierarchy of claims that include SEQ ID NOs instead of the name, ORF 8:

1. An isolated nucleic acid sequence comprising a polynucleotide that hybridizes (under particular, definite conditions) to SEQ ID NO:1, base pairs 57583-58854, wherein said polynucleotide encodes a protein (with a particular oxidase function as found in Table II).
2. The isolated nucleic acid sequence of Claim 1, wherein the sequence of said protein is SEQ ID NO:115.
3. The isolated nucleic acid sequence of Claim 2, wherein said polynucleotide is SEQ ID NO:1, base pairs 57583-58854.
4. The isolated nucleic acid sequence of Claim 3 that is SEQ ID NO:1.
5. Vector and host cell claims like those found in pending Claims 40-45.
6. Particular method claims using the nucleic acid sequences and/or vectors and/or host cells of particular claims above.

Examiner's Comments

37. The Examiner notes, as previously discussed in the Priority section, that the complete sequence of ORF 8 does not appear to have been disclosed in the priority documents. Applicants are invited to argue this point considering the fact that the ORF 8 primers are disclosed identically in both 60/118,848 and in the instant specification. However, maintaining that the sequence of ORF 8 (DNA encoding SEQ ID NO:115 or DNA that is SEQ ID NO:1 from 57583-58854) does not have priority, should Applicants amend the claims as suggested above by the Examiner, some of Applicants own art *may* become prior art under 35 U.S.C. § 102(a).

Conclusion

38. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK
March 7, 2002

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